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Comparing asthma treatment in elderly versus younger patients

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Summary
A randomised 6-month study compared two maintenance doses of budesonide/formoterol (Symbicort® Turbuhaler®)[h] maintenance and reliever therapy (Symbicort SMART®), 160/4.5 μg 1 × 2 and 2 × 2, in 8053 asthmatics with symptoms despite treatment with inhaled corticosteroids ± inhaled long-acting β_2-agonists. This analysis compared response to the two treatments in elderly patients, ≥65 years, with that in younger patients. Elderly patients with early- or late-onset asthma were also compared.

Elderly patients had lower post-bronchodilator FEV_1 percentage predicted normal at baseline than younger patients (85.6% vs. 91.0%, respectively). The elderly had more exacerbations and risk of first severe exacerbation was increased by 55.3% (hazard ratio 1.553; 95% confidence interval: 1.249–1.931, $p < 0.0001$). However, no differences in exacerbations were seen between 1 × 2 or 2 × 2 budesonide/formoterol maintenance and reliever therapy treatment in the elderly. Five-item Asthma Control Questionnaire (ACQ-5) scores improved equally in the two age groups. Changes in mean ACQ-5 scores between 1 × 2 and 2 × 2 were significant in both age groups but not clinically relevant (≥65 years, 0.12; $p = 0.018$; <65 years, 0.09; $p < 0.0001$). Elderly patients with early- and late-onset asthma responded equally well to treatment.

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[h] Neither the Symbicort SMART posology nor the dry powder formulation, Turbuhaler, is currently approved in the US.

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Budesonide/formoterol maintenance and reliever therapy (1 × 2 or 2 × 2) is an effective, well-tolerated and practical treatment concept in elderly and younger asthmatic patients.
Clinical trial registration: NCT00463866

Introduction

The World Health Organization has estimated a doubling of the world population of people over the age of 65 years (elderly) by the year 2025.[1] Asthma in the elderly is not a rare disorder[2] but may be misdiagnosed, especially as chronic obstructive pulmonary disease (COPD).[3] Approximately 50% of asthma deaths occur in the elderly.[4] Underdiagnosis has been recognised for some time[5] and remains a problem, resulting in poor treatment and impaired quality of life of the patients.[6,7] There is an increased focus on asthma in the elderly population.[8,9]

Traditionally, two phenotypes of asthma have been described in the elderly: early-onset asthma (EOA), starting before the age of 40 years, and late-onset asthma (LOA), starting later in life, after 40 years of age.[10] In EOA, atopy is more often detectable, whereas LOA is more often associated with respiratory tract infections, environmental inducers or other non-allergic factors. There is some evidence that elderly patients with EOA have poorer airway function compared with patients with LOA, whereas patients with LOA may show a more rapid decline over time in forced expiratory volume in 1 s (FEV_1).[11,12] Patients with EOA also usually have less reversible airway obstruction and poorer response to pharmacotherapy.[13] Other phenotypes have been identified and proposed in elderly asthmatics by the cluster analysis approach.[14,15]

From a pathophysiological point of view, there is no difference between asthma in the elderly and in the rest of the population.[16] What does differ between elderly and younger patients is the pharmacokinetics of drugs due to differences in the subjects' volume of distribution.[17] A decrease in response to interleukin-5 stimulation of peripheral blood eosinophils in elderly has also been reported.[18]

Differences reported between elderly and younger patients relate to clinical expressions of the disease; elderly patients are described as reporting fewer symptoms and using less medication.[19,20] Concerns have been raised about β_2-agonist response and side effects, osteoporosis with the use of inhaled corticosteroids (ICS), exacerbations of asthma due to medication for comorbid conditions or technical problems with inhalation devices.[19,20]

Few large clinical studies have compared the results of asthma therapies in the elderly with the rest of the asthma population,[9,10,20] reflecting the fact that elderly patients may be excluded from controlled clinical trials.

We have previously reported the results of a large pan-European budesonide/formoterol (Symbicort® Turbuhaler®) maintenance and reliever therapy (Symbicort SMART®) study.[9,21] This was an open-label, randomised 6-month study that compared two maintenance doses of budesonide/formoterol 160/4.5 μg one inhalation twice daily (bid; 1 × 2) and 160/4.5 μg two inhalations bid (2 × 2) in asthmatics over 18 years. In the total study population, the time to first severe asthma exacerbation was prolonged by 18% with 2 × 2 versus 1 × 2 (hazard ratio [HR] 0.82; $p = 0.03$). Low lung function (peak expiratory flow [PEF]) was found to be the only statistically significant predictor of a better response to 2 × 2. Among 8053 patients randomised and analysed for the primary endpoint, 1234 (15.3%) were ≥65 years old. As there are few large published asthma studies in the elderly population, we prospectively planned to perform additional analyses on this group.

The aim of this study was to analyse the baseline characteristics of the elderly subpopulation and their response to treatment compared with the younger reference population. Our hypothesis was that the elderly patients may respond less well to budesonide/formoterol maintenance and reliever therapy than the younger reference population and that the elderly would benefit more from the high maintenance dose strategy (2 × 2) compared with the standard maintenance treatment (1 × 2).

Materials and methods

Study subjects and design

Study subjects and design were as described previously.[21] Male and female patients with moderate to severe asthma, ≥18 years old, with a minimum of 6 months documented history of asthma according to the American Thoracic Society definition (ATS 1987), having asthma symptoms and a history of use of a rapid-acting β_2-agonist (a short-acting β_2-agonist [SABA] or formoterol) for symptom relief during the last month despite treatment with ICS or ICS plus a long-acting inhaled β_2-agonist (LABA) were recruited in 14 European countries into a 6-month open, randomised clinical trial. Patients should have been on maintenance therapy with ICS for at least 1 month at a constant daily dose of at least 500 μg beclomethasone dipropionate or an equivalent dose of any other ICS. Smokers could be enrolled; however, smokers over 40 years of age with a smoking history of 10 pack-years or more were excluded, as were patients with a diagnosis of COPD. There were four clinic visits in the study: at enrolment (Visit 1), randomisation (Visit 2), after treatment for 3 months (Visit 3) and at the end of the 6-month study (Visit 4). Among the 8053 randomised patients in the main EuroSMART study there were 1234 (15.3%) patients who were 65 years of age or older.

Assessments

Demographic and clinical data were collected at baseline. During the 2-week run-in period, and during 2-week periods prior to Visits 3 and 4, patients recorded in a notebook the number of inhalations taken as maintenance medication,

the number of reliever inhalations used, asthma symptoms during the day (yes/no) and night-time awakenings (yes/no) due to asthma. At Visits 2 and 4, lung function assessments were performed (FEV_1 and PEF). PEF only was performed if spirometry was not available. Patients were instructed in the inhalation technique at Visits 1 and 2. At Visit 2, their inhalation technique was observed by the investigator.

Reversibility tests were performed according to local practice and there was no demand for withholding SABA or LABA preparations before the tests.

The five-item Asthma Control Questionnaire (ACQ-5),[22–24] excluding FEV_1 (as FEV_1 was not measured at all clinics) and use of SABA (as budesonide/formoterol should be used as reliever medication) was recorded via self-administration at Visits 2, 3 and 4. The scale of each ACQ-5 component ranges from 0 to 6 (0 = best, 6 = worst). The ACQ-5 total scores were reported in three groups: mean scores less than 0.75 (well-controlled asthma), 0.75–1.5 (intermediate group) and greater than 1.5 (poorly controlled asthma). These intervals were based on data from a previous large clinical study.[25] Scores were also analysed according to the threshold for the minimal clinically meaningful difference of 0.5 score points.

The primary efficacy variable was time to first severe asthma exacerbation, defined as deterioration in asthma requiring oral or systemic corticosteroids either for at least 3 days, or leading to hospitalisation, emergency room visit or other patient-initiated unscheduled visits to a healthcare centre. Compliance with treatment was not formally monitored as the study aimed to mimic a real-life clinical practice. Safety was evaluated by reporting serious adverse events (SAEs) and adverse events leading to discontinuation (DAEs) from the study.

The study was performed according to Good Clinical Practice and the Declaration of Helsinki. All local ethics committees approved the study protocol. All patients gave their written informed consent for participation.

Determination of sample size

With a sample size of 4000 patients in each group of the main study and a significance level of 5%, the study had a 90% power to detect a reduction from 10% to 7.9% in the proportion of patients experiencing a severe asthma exacerbation during the 6-month study period. No stratification was performed related to age at randomisation. No separate power calculation was performed for this subgroup analysis.

Statistical analysis

Time to first severe asthma exacerbation was compared using a Cox proportional hazard model, stratified by country and with treatment as factor. The total number of severe exacerbations was compared between the treatments using a Poisson regression model controlling dispersion with country and treatment as factors and total time in study as an offset variable. The comparison between age groups was calculated using the same methods.

The change in ACQ-5 scores, daytime symptoms, night-time awakenings and lung function was analysed using an analysis of covariance model with treatment and country as factors and baseline value as covariate.

Results

Demography

Of the 9695 patients who were enrolled, 8424 were randomised, 8053 were included in the efficacy analysis and 8405 were included in the safety analysis. Baseline demographic characteristics of the elderly study population and the reference population are shown in Table 1. There were 1234 patients $\geq$65 years (15.3% of the study population) and 11% of the total study population were current smokers with a mean smoking history of 5.7 pack-years. The mean FEV_1 after bronchodilation in the elderly was 85.6% of their predicted normal, which was lower than the 91.0% predicted normal in the younger reference population. The elderly patients had significantly more asthma symptoms and were less controlled in their asthma assessed by ACQ-5 score. They also had significantly more comorbidities, especially ischaemic heart disease and hypertension. There were no notable important differences in baseline characteristics between elderly patients randomised to treatment with budesonide/formoterol 1 × 2 (n = 618) or 2 × 2 (n = 616).

Among the elderly patients, 231 (18.7%) had EOA (58% females) and 1003 (81.3%) had LOA (69% females). Patients with EOA had lower baseline post-bronchodilator FEV_1 (Table 1). Allergic rhinitis and allergic conjunctivitis were more prevalent among patients with EOA. Fig. 1 shows the presence of allergic rhinitis and allergic conjunctivitis in the entire study population in relation to age. Parameters reflecting asthma control such as symptoms, night-time awakenings, use of reliever medication and ACQ-5 scores were similar in the two groups.

Use of study medication

The mean doses of maintenance and reliever medication expressed as budesonide doses, in the elderly patients and in the reference group are shown in Table 2. Both maintenance and reliever usage was very similar in the two age groups. In both age groups, the total doses were higher in the 2 × 2 group and the as-needed doses were lower, compared to the 1 × 2 groups.

Exacerbations

During the 6-month study there were a total of 104 elderly patients with severe exacerbations compared with 379 patients with severe exacerbations in the reference population. The estimated yearly rate of exacerbations among the elderly was 25.1%, whereas the rate in the reference population was 15.4% ($p < 0.0001$).

The difference in time to first severe exacerbation between the two age groups, regardless of treatment, was statistically significant, with the risk of the first severe

Table 1 Demographic baseline data in elderly and younger asthmatics, and elderly asthmatics with early- and late-onset asthma.

Characteristics	Patients ≥65 years old $n = 1234$	Patients <65 years old $n = 6819$	*p*-value	Elderly patients with EOA $n = 231$	Elderly patients with LOA $n = 1003$	*p*-value
Females, %	67	61	<0.0001	58	69	0.0023
Age, years	71.6 (5.0)	43.5 (12.5)	N/A	70.8 (4.5)	71.7 (5.1)	0.0039
Non-smokers, %	77	67	N/A	75	77	0.6168
FEV_1, % predicted normal post-bronchodilation	85.6 (22.7)	91.0 (19.4)	<0.0001	81.0 (22.1)	86.6 (22.7)	0.0038
Reversibility, %	6.15 (13.5)	6.11 (12.9)	<0.0001	8.44 (12.4)	5.66 (13.6)	0.0159
PEF, % predicted normal post-bronchodilation	89.8 (28.8)	90.7 (24.0)	0.2958	85.2 (28.1)	90.8 (28.8)	0.0088
ICS dose at entry, μg/day	1114 (595)	1028 (582)	0.0560	1168 (658)	1102 (579)	0.2175
LABA use, % patients	81.7	78.6	0.0016	82.7	77.7	0.0938
SABA use, inhalations/day	1.66 (1.23)	1.49 (1.32)	<0.0001	1.76 (1.30)	1.64 (1.20)	0.2040
Days with symptoms/week	4.67 (2.18)	4.34 (2.13)	<0.0001	4.60 (2.20)	4.68 (2.20)	0.6214
No. of nights with awakenings/ week	1.24 (1.79)	1.11 (1.59)	0.0147	1.16 (1.80)	1.26 (1.80)	0.4439
ACQ-5 score at baseline	1.92 (1.02)	1.84 (0.99)	0.0127	1.85 (0.99)	1.94 (1.03)	0.2455
No. of exacerbations in past 12 months	1.31 (2.04)	1.47 (2.49)	0.0110	1.26 (1.61)	1.32 (2.12)	0.6536
Comorbidities, % of patients						
IHD	10	1.6	<0.0001	11	9	0.3837
Hypertension	43	15	<0.0001	43	43	0.9516
GERD	21	12	<0.0001	20	21	0.8946
Other	32	19	<0.0001	26	33	0.0595

Values shown are means (standard deviation) unless stated otherwise.
ACQ-5 = five-item Asthma Control Questionnaire; EOA = early-onset asthma; FEV_1 = forced expiratory volume in 1 s; GERD = gastro-oesophageal reflux disease; ICS = inhaled corticosteroids; IHD = ischaemic heart disease; LABA = long-acting β_2-agonist; LOA = late-onset asthma; N/A = not applicable; PEF = peak expiratory flow; SABA = short-acting β_2-agonist.

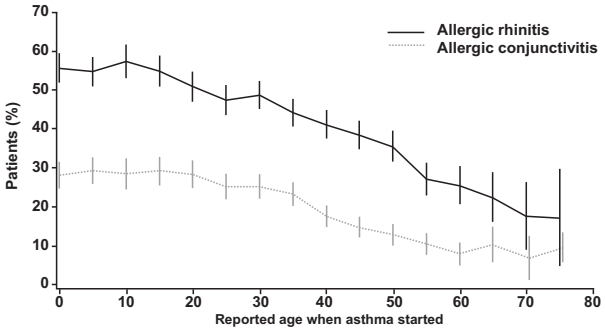

Figure 1 Prevalence (and 95% CI) of allergic rhinitis and allergic conjunctivitis in patients aged 18–96 years versus reported age when asthma started ($n = 8053$).

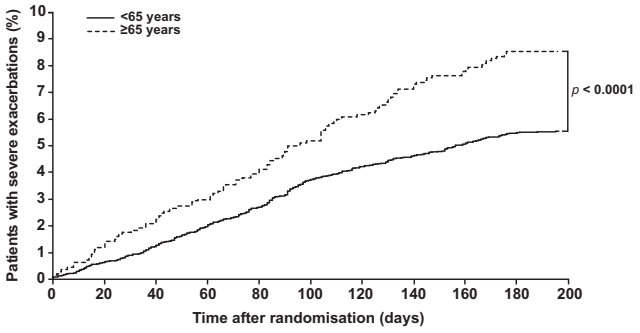

Figure 2 Time to first severe exacerbation in elderly patients (≥65 years of age) and in the reference group (<65 years of age).

exacerbation being increased by 55.3% in the elderly (HR 1.553; 95% confidence interval [CI]: 1.249–1.931; $p < 0.0001$) (Fig. 2). The time to first severe asthma exacerbation in the two age groups is shown in Fig. 3, for patients treated with 1 × 2 and 2 × 2. Although the time to first severe exacerbation was significantly prolonged in the remainder of the population studied, the younger age group, in favour of the 2 × 2 treatment (HR 0.797; 95% CI: 0.651–0.977; $p = 0.0286$), in the elderly population, the population of interest, there was no difference in time to first severe exacerbation between the groups treated with 1 × 2 or 2 × 2, respectively (HR 0.984; 95% CI: 0.666–1.454; $p = 0.934$).

Asthma control questionnaire

The reduction in ACQ-5 total scores in the elderly patients irrespective of treatment was 0.608 compared with 0.741 in the reference population. The difference in change of ACQ-5 between the age groups was 0.133 ($p < 0.0001$).

Divided by treatment, the changes in ACQ-5 scores both in the 1 × 2 and 2 × 2 groups were similar in the elderly and in the younger reference population (Table 3). The mean difference between 1 × 2 and 2 × 2 treatments was significant but small in both the elderly and the reference group ($p = 0.018$ and $p < 0.0001$, respectively).

Changes in ACQ-5 of more than 0.5 units are illustrated in Fig. 4. In the elderly patients a total of 49% improved more than 0.5 units and 9.5% deteriorated. With the 1 × 2 treatment, 44% of the elderly patients improved and 12% deteriorated by more than 0.5 units (corresponding figures in the reference population were 52% and 8%). With 2 × 2 treatment 54% improved and 7% deteriorated (56% and 7% in the reference population).

Changes from baseline in patient-reported outcomes

Asthma symptoms

The changes in days with asthma symptoms per week from baseline are shown in Table 3. Small differences were seen between the age groups and a similar response to the two randomised treatment groups.

Use of as-needed medication

Before the study all patients used a SABA as reliever medication. During the study they used budesonide/formoterol – the same inhaler as for maintenance therapy. There was a larger reduction in the usage of as-needed inhalations in the elderly group (Table 3).

Awakenings

The change in number of night-time awakenings per week from baseline is shown in Table 3. The difference between the age groups is small and a similar response to the two randomised treatments was observed.

Early- versus late-onset asthma

In the elderly, no difference in response to treatment (time to first severe asthma exacerbation, changes in asthma symptoms, night-time awakenings, use of reliever medication and ACQ-5) was observed between the EOA and LOA groups, in either the 1 × 2 or the 2 × 2 group (data not shown).

Table 2 Doses of budesonide used during the study.

BUD/FORM maintenance and reliever therapy, μg	Patients ≥65 years old		Patients <65 years old	
	1 × 2	2 × 2	1 × 2	2 × 2
Maintenance doses	317.3 (23.1)	635.2 (45.5)	317.6 (17.6)	634.7 (44.3)
As-needed doses	154.4 (175.6)	101.7 (146.7)	143.8 (177.5)	102.0 (145.6)
Total	471.6 (178.7)	736.8 (156.5)	461.4 (179.2)	736.5 (152.1)

Values shown are means (standard deviation).
BUD/FORM = budesonide/formoterol.

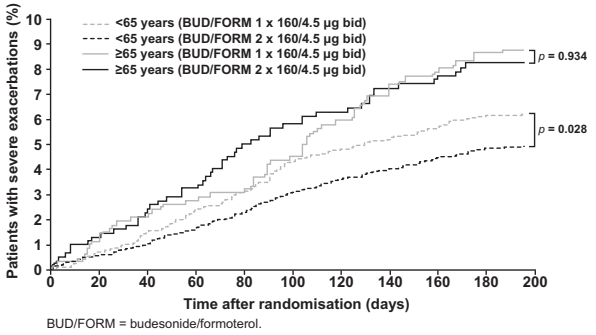

Figure 3 Time to first severe exacerbation in elderly patients (≥65 years of age) and in the reference group (<65 years of age) treated with budesonide/formoterol 160/4.5 μg one inhalation twice daily (bid; 1 × 2) or two inhalations bid (2 × 2).

Safety

SAEs were slightly more common in the elderly compared with the younger reference population. A total of 43 elderly patients reported an SAE (3.5%) compared with 122 (1.8%) in the reference population. Five SAE reports among elderly patients were linked to asthma worsening, compared with 19 such reports in the reference group. Two SAEs in the elderly group were considered related to treatment, both in the 2 × 2 group: one case of hypokalaemia, and another of tachycardia and muscle spasms. One elderly patient died during the study due to an intracranial haemorrhage which was considered to be unrelated to the study.

In the elderly population, there were 39 (3.2%) patients with DAEs compared with 124 patients (1.8%) in the reference population. In the 1 × 2 treatment group, there were 13 (2.1%) DAEs among the elderly compared with 57 (1.7%) in the reference population. In the 2 × 2 group the corresponding figures were 26 (4.2%) and 67 (2.0%), respectively. No elderly patients discontinued due to asthma worsening, but two elderly patients discontinued due to pneumonia.

The percentage of patients using more than eight inhalations per day (the highest recommended dose) of budesonide/formoterol (maintenance plus reliever use) was 1.9% among the elderly and 3.7% in the younger reference group.

Discussion

Our study showed that elderly asthmatics benefited from the asthma treatment strategy under investigation, budesonide/formoterol maintenance and reliever therapy, in a similar way to the younger reference group. No difference was found in the elderly population between standard maintenance (1 × 2) and maximum maintenance treatment (2 × 2), with respect to time to the first severe asthma exacerbation. As in the younger age group, mean ACQ-5 scores improved slightly more with the higher maintenance dose, but the difference in change between the treatments was not clinically relevant. No difference in response to treatment was seen between elderly patients with EOA or LOA.

This asthma study is one of the largest to include an elderly population, comprising more than 1200 patients with ages ranging from 65 to 96 years. The study gives important information regarding baseline characteristics in an elderly asthma population with moderate to severe symptomatic asthma.

There is a problem with underdiagnosis of asthma in the elderly[6,7] as COPD has to be considered as a differential diagnosis.[3] In our study protocol, patients with COPD were excluded from enrolment. Smokers were included only if they had a smoking history of less than 10 pack-years. It is likely, therefore, that we were reasonably successful in maintaining the homogeneity of the respiratory diagnosis. Elderly patients had a mean lung function within the normal range and they responded both in reversibility testing and treatment in a similar way to the younger reference population.

The time to first severe asthma exacerbation was significantly shorter for elderly asthmatics compared with the reference population, but we did not find a difference between the higher maintenance (2 × 2) treatment and the standard maintenance treatment (1 × 2) notwithstanding the lower treatment load in the 1 × 2 group. This was despite elderly patients having more symptoms and lower lung function at study entry. In our primary paper,[21] age was a poor predictor of requirement for the maximum maintenance dose; the improvements from baseline in patient-reported outcomes, i.e. asthma symptoms, night-time awakenings and use of reliever medication, were of the same degree in the elderly patients compared with the rest of the study population. ACQ-5 improved in the elderly as in the younger population and the improvements with 2 × 2 were significantly greater than with 1 × 2, although numerically small and without clinical importance.

No difference in responses to budesonide/formoterol maintenance and reliever therapy was seen between patients with EOA and LOA, either in the 1 × 2 or in the 2 × 2 treatment group.

This subgroup analysis showed that elderly patients were somewhat more symptomatic, used higher doses of ICS and

Table 3 Response to treatment in elderly asthmatics compared with the response in patients aged <65 years.

Response to BUD/FORM maintenance and reliever therapy	Patients ≥65 years old		Patients <65 years old	
	1 × 2	2 × 2	1 × 2	2 × 2
Change in ACQ-5	−0.59	−0.71	−0.69	−0.78
Change in days with asthma symptoms/week	−1.62	−2.21	−1.57	−2.12
Change in as-needed inhalations[a]	−0.71	−1.04	−0.60	−0.86
Change in night-time awakenings/week	−0.47	−0.58	−0.44	−0.57

ACQ-5 = five-item Asthma Control Questionnaire; BUD/FORM = budesonide/formoterol.
[a] Change from SABA doses to budesonide/formoterol doses.

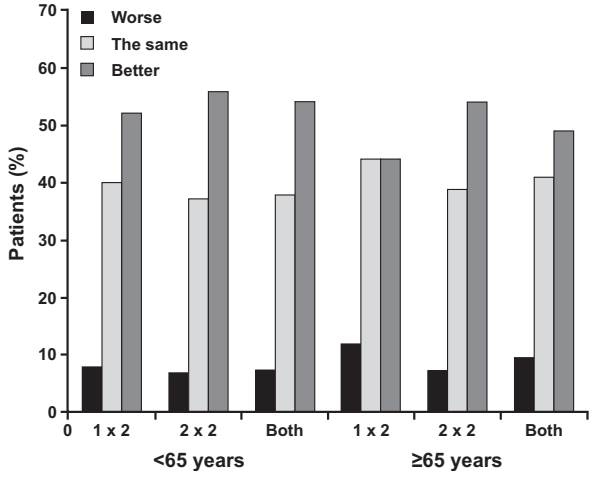

Figure 4 Clinically important shifts (change of >0.5) from baseline to treatment in ACQ-5 scores in elderly patients and in the reference group, and separately for patients treated with budesonide/formoterol 160/4.5 μg one inhalation bid (1 × 2) or two inhalations bid (2 × 2).

more reliever medication, and suffered more often from comorbidities compared with the younger reference group. These findings differ from earlier reports on asthma in the elderly, which state that elderly asthmatics often do not report symptoms to the same degree as younger patients as they are "poor perceivers" of symptoms.[26,27] A reason for this discrepancy is perhaps the inclusion criterion of our study requiring patients to use a reliever inhaler for the alleviation of symptoms at study entry.

Regarding the usefulness of the budesonide/formoterol maintenance and reliever therapy in elderly patients, it was found that the elderly appeared to manage the regimen equally as well as younger patients in this clinical trial performed in a real-life setting. The elderly patients used similar numbers of as-needed inhalations as the reference group, indicating that the treatment concept was equally well implemented in the two age groups. This was also supported by the changes in ACQ-5 scores and the reductions in days with asthma symptoms per week which were similar in the elderly compared with the reference group.

Although statistically significant, no clinically important differences were found in the shifts in ACQ-5 scores between the elderly and the younger patients. Almost the same proportion of elderly patients reported the clinically important change of 0.5 score units as the younger patients. In this study, the FEV_1 question was excluded from the ACQ assessment as spirometry was not performed in all centres. In other large studies the exclusion of FEV_1 and use of short-acting bronchodilators did not alter the validity and measurement properties of the questionnaire.[24,28] In the absence of spirometry reference values for patients over 75 years old, the European Community of Coal and Steel (ECCS)/ERS values were used.[29] This has probably led to some overestimation of bronchial obstruction in this age group.

The distribution of patients with allergic rhinitis and/or allergic conjunctivitis in relation to age at onset of asthma (Fig. 1) clearly demonstrates a higher prevalence in younger patients. Despite this finding, it is of note that elderly patients with either EOA or LOA responded equally well to treatment with budesonide/formoterol; perhaps distinguishing between these two phenotypes is of minor importance from a pharmacological view. The slightly lower lung function among patients with EOA compared with LOA is in agreement with earlier reports.[11,12] However, this lower baseline lung function was not reflected in EOA patients experiencing more symptoms. The improvements in lung function from baseline corresponded to the degree of reversibility at baseline, i.e. the improvement was slightly greater in the EOA group.

Although more elderly patients reported SAEs than the younger patients, this was not linked to asthma worsening (only 5 out of 43 SAEs were related to asthma). The proportion of elderly patients using more than the recommended maximum daily dose was lower than in younger patients. The steroid load during the study, especially in the 1 × 2 group, was markedly reduced; this may have beneficial safety implications, although strong conclusions cannot be drawn in the absence of a parallel reference cohort. Use of the lowest effective dose of ICS to control asthma is even more important in the elderly, where there are concerns regarding long-term use of high doses of ICS.

We conclude that budesonide/formoterol maintenance and reliever therapy is a well-tolerated and manageable treatment concept in elderly asthmatics. The inhaled steroid load was not higher in the elderly group compared with the younger reference population. The risk of having a first exacerbation was greater in the elderly, but no difference was seen between patients treated with budesonide/formoterol 1 × 2 and 2 × 2. ACQ-5 improved equally in the two age groups. Elderly patients with early- or late-onset asthma responded equally to treatment. Despite the absence of difference in exacerbations between the two maintenance doses and the lack of a reliable reference value for lung function data in the elderly population, the level of post-bronchodilator lung function should always be considered.[21]

Conflicts of interest

J. Haughney has received reimbursements for attending symposia, fees for speaking and organising educational events, funds for research and fees for consulting from AstraZeneca. He has also received support from a number of pharmaceutical companies (Boehringer Ingelheim, GlaxoSmithKline, Merck Sharp & Dohme, Mundipharma, Novartis, Nycomed, sanofi-aventis and Teva).

M. Aubier has participated as a speaker in scientific meetings or courses organised and financed by various pharmaceutical companies (GlaxoSmithKline, AstraZeneca, Novartis, Pfizer, and Nycomed).

J. Ostinelli and L. Jørgensen are full-time employees of, and hold stock in, AstraZeneca.

C.P. van Schayck has received a fee for consulting from AstraZeneca.

O. Selroos has received consultation fees from AstraZeneca and Galenica, fees for speaking at medical meetings organised by AstraZeneca and fees for drafting publications

for AstraZeneca, Orion Pharma and Schering-Plough. He also holds stock in AstraZeneca.

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